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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/016,752	10/30/2001	Ramy Lidor-Hadas	1662/55002	8981

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EXAMINER	
OH, TAYLOR V	
ART UNIT	**PAPER NUMBER**
1625	

DATE MAILED: 04/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/016,752	LIDOR-HADAS ET AL.	
	Examiner	Art Unit	
	Taylor Victor Oh	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-8,20-22,25-39,41,43,45-70 and 72-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-8,20-22,25-39,41,43,45-70 and 72-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/3/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/2/06 has been entered.

The Status of Claims

Claims 5-8, 20-22, 25-39, 41, 43, 45-70, and 72-91 are pending.

Claims 5-8, 20-22, 25-39, 41, 43, 45-70, and 72-91 are rejected.

Priority

1. It is noted that the application claims benefit of 60/244,283 (10/30/2000), 60/253,819(11/29/2000), and 60/265,539 (01/31/2001).

Drawings

2. The drawings filed on 10/30/2001 are accepted by the examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 89-91 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a pharmaceutical composition comprising the various polymorphic forms of ondansetron hydrochloride. According to the specification, there are some remarks about various polymorphic forms of the ondansetron hydrochloride, but there are no other information about which polymorphic form in the pharmaceutical composition is effective regarding its bioavailability, drug absorption, rate of dissolution, elimination rate, and stability during the preparations. It is not uncommon to find several polymorphs of compounds existing under normal handling conditions. Just as every polymorph has its unique characteristic X-ray patterns, so does every solvate. Many different polymorphs and /or solvates show varying dissolution rates. Therefore, on the time scale of the pharmaceutical bioavailability, different total amounts of drug are dissolved, resulting in potential bio-inequivalence among the several forms of the drug. Since these aspects are absent in the specification, the skilled artisan in the art is unable to determine which polymorphic form of ondansetron hydrochloride in the pharmaceutical composition is effective for the pharmaceutically acceptable bioavailability. Therefore, an appropriate correction is required.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 45, 66, and 83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 45 and 66, the claims are directed to the anhydrous ondansetron hydrochloride compound ,but it contains water. This is vague and indefinite because the compound claims are written as if the composition claims. Therefore, an appropriate correction is required.

In claim 83, the terms " substantially dry" is recited. Thsie expression is vague and indefinite because the specification does not elaborate what is meant by the terms " substantially dry". Therefore, an appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 5 – 7, and 19-20 are rejected under 35 U.S.C. 102(b) as being anticipated clearly by Wu Gousheng et al (CN 1113234 , translation version).

Wu Gousheng et al discloses a 1,1,2,2,3-pentahydrogen-9-methyl-3((2'-methyl-imidazole-1)-methyl)-4-oxocarbazole hydrochloride monohydrate compound (see page 16 on its translation ,lines 20-22); furthermore, an organic base and standard physiological salt and solvate can be incorporated into the compound in order to be used as a medication for treating nausea and vomiting (see abstract). Concerning the production of the 1,1,2,2,3-pentahydrogen-9-methyl-3((2'-methyl-imidazole-1)-methyl)-4-oxocarbazole hydrochloride dihydrate compound, the following steps can be used:

1. dissolving the compound of 1,1,2,2,3-pentahydrogen-9-methyl-3((2'-methyl-imidazole-1)-methyl)-4-oxocarbazole in 5 ml of ethanol;
2. blowing dry HCl into the solution;
3. cooling down the resultant mixture, crystallizing the compound , and recrystallizing it with water , thereby obtaining the 1,1,2,2,3-pentahydrogen-9-methyl-3((2'-methyl-imidazole-1)-methyl)-4-oxocarbazole hydrochloride dihydrate compound (see page 21 , lines 8-17).

Furthermore, in order to isolate the 1,1,2,2,3- pentahydrogen-9-methyl-3((2'-methyl-imidazole-1)-methyl)-4-oxocarbazole hydrochloride monohydrate compound, the 1,1,2,2,3-pentahydrogen-9-methyl-3((2'-methyl-imidazole-1)-methyl)-4-oxocarbazole hydrochloride dihydrate compound is recrystallized with water and dried in a drier containing P_2O_5 (see page 17 , lines 16-17).

This is identical with the claims.

4. Claims 62-65 are rejected under 35 U.S.C. 102(b) as being anticipated clearly by Coates et al (GB 2153821).

Coates et al teaches the preparation of producing Ondansetron hydrochloride using isopropanol solvent in the following example (see page 16, lines 1-10):

EXAMPLE 10
1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1*H*-imidazol-1-yl)methyl]-4*H*-carbazol-4-one (18.3g) in a hot mixture of isopropanol (90ml) and water (18.3ml) was treated with concentrated hydrochloric acid (6.25ml). The hot mixture was filtered and the filtrate diluted with isopropanol (90ml) and stirred at room temperature for 17h, cooled to 2° and the solid filtered off (21.6g). A sample (6g) was recrystallized from a mixture of water (6ml) and isopropanol (10ml) to give the *title compound* as a white crystalline solid (6g) m.p. 178.5-179.5°. Analysis Found:C,59.45; H,6.45; N,11.5.

Furthermore, Ondansetron hydrochloride form E mono- and/ or hemi-isopropanolate is inherently formed during the process. This is identical with the claims.

5. Claims 72-73 are rejected under 35 U.S.C. 102(b) as being anticipated clearly by Budavari (The Merck Index, 12 ed., p. 6977).

Budavari teaches the preparation of producing Ondansetron hydrochloride using methanol solvent (see page 6977). This is identical with the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 5-8, 20-22, 25-39, 41, 43, 45-70, and 72-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu Gousheng et al (CN 1113234 , translation version) in view of Llacer et al (International Journal of Pharmaceutics 177 (1999), p. 221-229).

Wu Gousheng et al discloses a 1,1,2,2,3-pentahydrogen-9-methyl-3((2'-methyl-imidazole-1)-methyl)-4-oxocarbazole hydrochloride monohydrate compound (see page 16 on its translation ,lines 20-22); furthermore, an organic base and standard physiological salt and solvate can be incorporated into the compound in order to be used as a medication for treating nausea and vomiting (see abstract). Concerning the production of the 1,1,2,2,3-pentahydrogen-9-methyl-3((2'-methyl-imidazole-1)-methyl)-4-oxocarbazole hydrochloride dihydrate compound, the following steps can be used:

1. dissolving the compound of 1,1,2,2,3-pentahydrogen-9-methyl-3((2'-methyl-imidazole-1)-methyl)-4-oxocarbazole in 5 ml of ethanol;
2. blowing dry HCl into the solution;
3. cooling down the resultant mixture, crystallizing the compound , and recrystallizing it with water , thereby obtaining the 1,1,2,2,3-pentahydrogen-9-methyl-3((2'-methyl-imidazole-1)-methyl)-4-oxocarbazole hydrochloride dihydrate compound (see page 21 , lines 8-17).

Furthermore, in order to isolate the 1,1,2,2,3- pentahydrogen-9-methyl-3((2'-methyl-imidazole-1)-methyl)-4-oxocarbazole hydrochloride monohydrate compound, the 1,1,2,2,3-pentahydrogen-9-methyl-3((2'-methyl-imidazole-1)-methyl)-4-oxocarbazole hydrochloride dihydrate compound is recrystallized with water and dried in a drier containing P_2O_5 (see page 17 , lines 16-17).

Moreover, there is a general procedure for producing the 1,1,2,2,3-pentahydrogen-9-methyl-3((2'-methyl-imidazole-1)-methyl)-4-oxocarbazole hydrochloride with an aqueous solvent by dissolving the 1,1,2,2,3- pentahydrogen-9-methyl-3((2'-methyl-imidazole-1)-methyl)-4-oxocarbazole to a water /alcohol solvent and adding hydrogen chloride (1N) to the resultant mixture to produce the desired compound (see page 8 , lines 19-24).

However, the instant invention differs from the prior art in that the claimed process is involved in using a solvent system ,such as ketone, toluene, xylene, ether, methanol; the exposure is for a period of three weeks or less or 30 to 70 hours; the

temperature is from -15^0 C to room temperature; and the mechanical agitation is sonification.

Llacer et al discloses the formation of ondansetron polymorphs by using different solvents ,such as acetone, chloroform , benzene, cyclohexane, ethanol ,and methanol (table 1) (see page 222, right col. at the top) under various temperatures and time (40—170^0 C ; 5 mins to 24 hr).

Concerning the use of the various solvent system for producing the desired compound, the reference is silent about them. However, the Wu Gousheng et al does indicate the use of benzene and n-propanol, which are similar to the functionality of the claimed solvents. Therefore, there is no patentable weight over the prior art reference in the absence of an unexpected result using the claimed solvent system.

With respect to the exposing period of three weeks or less or 30 to 70 hours and the temperature is from -15^0 C to room temperature, the limitation of a process with respect to ranges of pH, time and temperature does not impart patentability to a process when such values are those which would be determined by one of ordinary skill in the art in achieving optimum operation of the process. Temperature and period are well understood by those of ordinary skill in the art to be a result-effective variable, especially when attempting to control selectivity of a chemical process.

Regarding the use of the mechanical agitation by a sonic vibration, this is directly related to mechanical expediency. Therefore, it would have been obvious to the skilled artisan in the art to have motivated to employ the sonic vibration as mechanical expediency in order to accelerate the process.

Wu Gousheng et al does teach the general procedure for producing Ondansetron hydrochloride using the aqueous alcoholic solvent; similarly, Llacer et al expressly discloses the formation of ondansetron polymorphs by using various solvents ,such as acetone, chloroform , benzene, cyclohexane, ethanol ,and methanol (table 1) (see page 222, right col. at the top) under various temperatures and time (40-170^0 C ; 5 mins to 24 hr). Llacer et al has offered guidance that it is possible to form the different ondansetron polymorphs by using various solvents ,such as acetone, chloroform , benzene, cyclohexane, ethanol ,and methanol (table 1); furthermore, there is a teaching of equivalence between them regarding the use of alcoholic solvent. Therefore, it would have been obvious to the skilled artisan in the art to be motivated to incorporate the teachings of Llacer's et al various solvents into the Wu Gousheng et al process in order to produce various polymorphs of the Ondansetron hydrochloride.

7. Claims 5-8, 20-22, 25-39, 41, 43, 45-70, and 72-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coates et al (GB 2153821) in view of Llacer et al (International Journal of Pharmaceutics 177 (1999), p. 221-229).

Coates et al teaches the preparation of producing Ondansetron hydrochloride using various solvents in the following examples (see page 7 , lines 55-63; page 16, lines 1-10):

EXAMPLE 1a

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride

A solution of the product of Preparation 2 (2.0g) and 2-methylimidazole (5.0g) in dry dimethylformamide (30ml) was stirred, under nitrogen, at 95° for 16.75h and then allowed to cool. The solid that crystallised was filtered off, washed with ice-cold, dry dimethylformamide (3×2ml) and dry ether (2×10ml) and then dried. The resulting solid (0.60g) was suspended in a mixture of absolute ethanol (30ml) and ethanolic hydrogen chloride (1ml), and warmed gently to obtain a solution, which was filtered whilst warm. The filtrate was then diluted with dry ether to deposit a solid (0.6g) which was recrystallised from absolute ethanol to give the *title compound* as a solid (0.27g) m.p. 186-187°.

EXAMPLE 10

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1*H*-imidazol-1-yl)methyl]-4*H*-carbazol-4-one (18.3g) in a hot mixture of isopropanol (90ml) and water (18.3ml) was treated with concentrated hydrochloric acid (6.25ml). The hot mixture was filtered and the filtrate diluted with isopropanol (90ml) and stirred at room temperature for 17h, cooled to 2° and the solid filtered off (21.6g). A sample (6g) was recrystallized from a mixture of water (6ml) and isopropanol (10ml) to give the *title compound* as a white crystalline solid (6g) m.p. 178.5-179.5°. Analysis Found:C,59.45; H,6.45; N,11.5.

Furthermore, the active ingredient is micronized in a fluid energy mill to a fine particle size range prior to blending with normal grade tabletting lactose in a high energy mixer (see page 21 ,lines 55-56).

However, the instant invention differs from the prior art in that the claimed process is involved in using a solvent system ,such as ketone, toluene, xylene, ether, methanol; the exposure is for a period of three weeks or less or 30 to 70 hours; the temperature is from –150 C to room temperature; and the mechanical agitation is sonification.

Llacer et al discloses the formation of ondansetron polymorphs by using different solvents ,such as acetone, chloroform , benzene, cyclohexane, ethanol ,and methanol (table 1) (see page 222, right col. at the top) under various temperatures and time (40—170^0 C ; 5 mins to 24 hr).

With respect to the exposing period of three weeks or less or 30 to 70 hours and the temperature is from –15^0 C to room temperature, the limitation of a process with respect to ranges of pH, time and temperature does not impart patentability to a process when such values are those which would be determined by one of ordinary skill in the art in achieving optimum operation of the process. Temperature and period are well understood by those of ordinary skill in the art to be a result-effective variable, especially when attempting to control selectivity of a chemical process.

Regarding the use of the mechanical agitation by a sonic vibration, this is directly related to mechanical expediency. Therefore, it would have been obvious to the skilled artisan in the art to have motivated to employ the sonic vibration as mechanical expediency in order to accelerate the process.

Coates et al teaches the preparation of producing Ondansetron hydrochloride using ethanol and isopropanol ; similarly, Llacer et al expressly discloses the formation of ondansetron polymorphs by using various solvents ,such as acetone, chloroform , benzene, cyclohexane, ethanol ,and methanol (table 1) (see page 222, right col. at the top) under various temperatures and time (40-170^0 C ; 5 mins to 24 hr). Llacer et al has

offered guidance that it is possible to form the different ondansetron polymorphs by using various solvents ,such as acetone, chloroform , benzene, cyclohexane, ethanol ,and methanol (table 1); furthermore, there is a teaching of equivalence between them regarding the use of alcoholic solvent. Therefore, it would have been obvious to the skilled artisan in the art to be motivated to incorporate the teachings of Llacer's et al various solvents into the Coates et al process in order to produce various polymorphs of the Ondansetron hydrochloride.

8. Claims 5-8, 20-22, 25-39, 41, 43, 45-70, and 72-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Collin (EP 0415522) in view of Llacer et al (International Journal of Pharmaceutics 177 (1999), p. 221-229).

Collin teaches a process for reducing the crystal size of Ondansetron hydrochloride dehydrate in the following example (see page 3 ,lines 15-45).

Example 1

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate wherein the crystals are less than 250µm

A solution of 1,2,3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4 H -carbazol-4-one (147g) in a mixture of isopropanol (670mℓ), water (250mℓ) and glacial acetic acid (76mℓ) at ca . 80° was clarified by filtration and diluted with more water (61mℓ) and isopropanol (650mℓ). The solution was treated at 70° with 36%w/w hydrochloric acid (48mℓ) and cooled to ca. 5°. The resulting suspension was filtered and the filtered solid was washed by displacement with isopropanol (600mℓ) to give a solvent wet solid (269g). A portion of this solid (91g) was dried at ca. 50° and 200 torr for ca. 18h to give a solid (55g).

A portion of the dried solid (26g) was placed in a current of humidified air at ambient temperature until there was no further gain in weight and the title compound (29g) was obtained.

Particle Size Distribution of Title Compound	
Size (µm)	Cumulative % Undersize (by weight)
45	43.4
63	83.7
90	97.6
125	98.4
180	99.6
250	100.0

It is possible by means of the process according to the invention to reduce the crystal size of ondansetron hydrochloride dihydrate to the extent that the entire drug substance consists of particles of a sufficiently small size (i.e. less than 250µm, of which typically about 80% by weight are less than 63µm) to give an homogeneous distribution of the drug substance in the tablet blend.

Preferably, the ondansetron hydrochloride dihydrate obtained by crystallisation is desolvated by heating at a temperature greater than 40° C (e.g. 50° C) and at reduced pressure (e.g. 200 torr or less) for more than 8 hours. Alternatively, the ondansetron hydrochloride dihydrate obtained by crystallisation may be desolvated at ambient pressure by heating at a temperature of 50° C or above (more preferably 100° C).

Most preferably, ondansetron hydrochloride dihydrate obtained by crystallisation is desolvated by heating at 50° C at a pressure of 100 torr for 2 hours.

The desolvation process may be carried out with or without mechanical agitation.

The resultant ondansetron hydrochloride of reduced crystal size is then rehydrated, for example, by placing it in a humidified atmosphere of, for example, air or nitrogen, at ambient temperature. Rehydration will generally be continued until there is no further gain in weight.

(see page 2 ,lines 50-57 and page 3 ,lines 1-3).

However, the instant invention differs from the prior art in that the claimed process is involved in using a solvent system ,such as ketone, toluene, xylene, ether, methanol; the exposure is for a period of three weeks or less or 30 to 70 hours; the temperature is from –150 C to room temperature; and the mechanical agitation is sonification.

Llacer et al discloses the formation of ondansetron polymorphs by using different solvents ,such as acetone, chloroform , benzene, cyclohexane, ethanol ,and methanol

(table 1) (see page 222, right col. at the top) under various temperatures and time (40—170^0 C ; 5 mins to 24 hr).

With respect to the exposing period of three weeks or less or 30 to 70 hours and the temperature is from -15^0 C to room temperature, the limitation of a process with respect to ranges of pH, time and temperature does not impart patentability to a process when such values are those which would be determined by one of ordinary skill in the art in achieving optimum operation of the process. Temperature and period are well understood by those of ordinary skill in the art to be a result-effective variable, especially when attempting to control selectivity of a chemical process.

Regarding the use of the mechanical agitation by a sonic vibration, this is directly related to mechanical expediency. Therefore, it would have been obvious to the skilled artisan in the art to have motivated to employ the sonic vibration as mechanical expediency in order to accelerate the process.

Collin et al does teach the general procedure for producing Ondansetron hydrochloride using the aqueous alcoholic solvent; similarly, Llacer et al expressly discloses the formation of ondansetron polymorphs by using various solvents ,such as acetone, chloroform , benzene, cyclohexane, ethanol ,and methanol (table 1) (see page 222, right col. at the top) under various temperatures and time (40-170^0 C ; 5 mins to 24 hr). Llacer et al has offered guidance that it is possible to form the different ondansetron polymorphs by using various solvents ,such as acetone, chloroform , benzene, cyclohexane, ethanol ,and methanol (table 1); furthermore, there is a teaching of equivalence between them regarding the use of

alcoholic solvent. Therefore, it would have been obvious to the skilled artisan in the art to be motivated to incorporate the teachings of Llacer's et al various solvents into the Wu Gousheng et al process in order to produce various polymorphs of the Ondansetron hydrochloride.

Applicants' Argument

Concerning the applicants' arguments, the examiner has considered them; however, since the examiner has applied new prior art to the claimed invention, it seems proper that the examiner will respond to the applicants' arguments after applicants' review on the rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taylor Victor Oh whose telephone number is 571-272-0689. The examiner can normally be reached on 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

*** 4/12/06